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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,684	11/08/2001	Aristo Vojdani	IMSCI2.005A	9590

20995 7590 12/15/2004

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EXAMINER	
YANG, NELSON C	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,684	VOJDANI, ARISTO	
	Examiner	Art Unit	
	Nelson Yang	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendment of claim 1 and addition of claim 12 is acknowledged and has been entered.

2. Claims 1-12 are currently pending.

Rejections Withdrawn

3. Applicant's arguments, see pages 4-5, filed September 23, 2004, with respect to rejection of claims 1, 2, 10, 11, under 35 U.S.C. 112, second paragraph, have been fully considered and are persuasive. The rejection of said claims under 35 U.S.C. 112, second paragraph, has been withdrawn.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. The preamble of claim 1 recites a method for distinguishing possible autoimmunity from possible cardiovascular disease with autoimmune disease in a patient. However, the steps appear to be directed toward distinguishing the presence or possibility of autoimmune disease from the presence or possibility of cardiovascular disease and autoimmune disease, rendering the claim

unclear and indefinite, as autoimmunity and autoimmune disease are not necessarily the same thing.

7. The term "possible" in claim 1 is a relative term which renders the claim indefinite. The term "possible" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

8. Specifically, it is unclear how statistically accurate this method is at determining and distinguishing autoimmunity and cardiovascular disease with autoimmune disease. It is unclear how likely someone distinguished with possible autoimmuninity or cardiovascular disease with autoimmune disease will actually have autoimmunity or cardiovascular disease with autoimmune disease. How likely is someone who is distinguished with possible autoimmunity from possible cardiovascular disease with autoimmune disease develop autoimmunity instead of cardiovascular and autoimmune disease? If a patient is distinguished with possible autoimmunity, does this mean that the patient will not develop a cardiovascular disease? If the patient is diagnosed for the possibility of autoimmune disease and cardiovascular disease, will the patient develop both diseases?

9. The term "normal" in claim 1 is a relative term which renders the claim indefinite. The term "normal" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Although applicant has defined in the specification that normal refers to the average level of antibody taken from a set of healthy control individuals, there remain issues that render the

term indefinite. In particular, it is unclear how the healthy control individuals were selected, and what parameters were used in the selection to provide the "normal" classification. For example patient 18 from table 3 on page 23 was classified as a healthy control, yet his numbers are all higher than normal, rendering it unclear why this patient was considered a healthy control.

It is also unclear if statistical and clinical significance are to be taken into account. At what levels of antibodies would the difference in levels between the test subjects' antibodies and the normal levels be considered clinically insignificant? While it is understood that the patients tested only had known risk factors for the diseases and would not necessarily have the diseases, it is unclear if further clinical studies were performed to establish whether the patients with negative results were not false negatives, and those with positive results were not false positives. Specifically, it is unclear if the selection of the patients was based on the positive ANA titer and the rheumatoid factor, or additional factors were used.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Specifically, applicant fails to teach a method where the level of a first set of antibodies associated with cardiovascular disease and a second set of antibodies different from

the first set associated with autoimmune disease are determined and compared with each other to distinguish the presence or possibility of either autoimmunity or autoimmune disease from the presence or possibility of autoimmune disease and cardiovascular disease. While applicant provides data showing possible autoimmunity as well as data showing possible cardiovascular and autoimmune disease, applicant does not disclose the steps of comparing the data to establish possible cardiovascular and autoimmune disease from possible autoimmune disease, or comparing the data to establish possible cardiovascular and autoimmune disease from possible autoimmunity.

12. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for detecting antibodies against certain antigens and for indicating the presence or possibility of autoimmune disease, does not reasonably provide enablement for a method for distinguishing possible autoimmune disease from possible cardiovascular disease with autoimmune disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make or use the invention commensurate in scope with these claims. The specification, according page 24, merely refers to fig. 6 for diagnosing possible autoimmunity, and data interpretation of antibody levels to human target antigens relating to the possible autoimmunity. Neither does figure 6 establish that higher than normal levels of all antibodies associated with cardiovascular disease would indicate the presence or possibility of autoimmune disease and cardiovascular disease, while higher than normal levels of all antibodies associated with autoimmune disease but not antibodies associated with cardiovascular disease would indicate the presence or possibility of autoimmune disease, as in figure 6, as applicant has only performed studies on 8 specific

antigens: myosin, oxidized LDL, heat shock protein 60 antibody, B-2 glycoprotein-1 antibody, immune complexes, arthritis peptides, and lupus peptides. Therefore, applicant would only be enabled at best for these 8 antigens.

The specification teaches the detection of salivary IgA against several antigens that are alleged to be related to autoimmune disease. Any elevation in the level of IgA in patients' samples as compared to normal control subjects would therefore indicate possible autoimmune or cardiovascular disease, depending on the antigens involved. Therefore even patients previously indicated as healthy (see patient 18 in table 3) would actually have possible autoimmune disease or possible cardiovascular disease. Therefore, it is unclear if this method actually even works, particular since it has not even been established what is meant by possible autoimmunity, possible autoimmune disease, or possible cardiovascular disease.

According to Strongin (Strongin, Sensitivity, specificity, and predictive value of diagnostic tests: definitions and clinical applications, 1993, Laboratory Diagnosis of Viral Infections, p. 211-219), a number of characteristics need to be considered in the development of any suitable diagnostic assay. These characteristics include the sensitivity of the assay, the true-positive test rate, the false-negative test rate, the specificity, the true-negative test rate, the false positive test rate, the predictive value, the prevalence, the efficiency or percentage of all results that are true, and the accuracy of the recited diagnostic assay. However, none of these characteristics appear to have been considered.

Additional considerations must also be examined to enable the clinician to practice the invention, including assessment of when the maximum sensitivity, maximum specificity, and

maximum efficiency are desired, how is the maximum sensitivity or specificity achieved, and how is the predictive value maximized. An essential understanding of these factors is required to enable the skilled artisan to accurately use and interpret any given diagnostic test. Specifically, the specification fails to disclose what is meant by the possibility of autoimmune disease or by the possibility of cardiovascular disease with autoimmune disease. Specifically, it is unclear how statistically significant are the results of this method.

13. Furthermore, it should be noted that based on the specification, particularly the data from figure 6, it would appear that higher than normal levels of antibodies associated with autoimmune disease and not cardiovascular disease such as immune complexes, lupus peptides antibodies, and arthritic peptides antibody would indicate possible autoimmunity and not possible autoimmune disease, as applicants are now claiming in the steps of claim 1. As a result, fig. 6 merely establishes a test for possible autoimmunity (and not the presence or possibility of autoimmune disease) and a separate test for possible cardiovascular disease and autoimmune disease. Since the specification lacks any teaching of a method for distinguishing the presence or possibility of autoimmune disease from the presence or possibility of cardiovascular disease with autoimmune disease in a patient, or any information regarding the patients from which the samples were taken, and whether any considerations were given to any of the characteristics stated above, it would require undue experimentation for one skilled in the art to make and use the invention as claimed.

Because of the lack of description in the specification for the claimed method, the data presented in tables 2 and 3, which provide data from patients with possible autoimmune disease

and healthy controls, and the examples do not allow the conclusive determination that anyone or everyone who has an elevated level of IgA to lupus peptides, arthritis peptides, or immune complexes has possible autoimmune disease, possible autoimmunity, or possible cardiovascular and autoimmune disease.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

14. Claims 1 and 3-9 are further rejected because the specification is not enabling for a method of detecting antibodies against any and all antigens. Specifically, the specification discloses the detection of IgA against lupus peptides, arthritis peptides, and certain immune complexes, comparing the detected level to those of normal control subjects and any elevation in the level of IgA is diagnostic for a possibility of autoimmune disease.

While the specification discloses the use of lupus peptides, arthritis peptides, and certain immune complexes for autoimmune disease, seen on pages 7-9, and of myosin, oxidized LDL, heat shock protein 60 antibody, B-2 glycoprotein-1 antibody, in addition to immune complexes, arthritis peptides and lupus peptides for cardiovascular disease, as seen in fig. 6, the specification fails to disclose any other antigens as being diagnostic for autoimmune disease. Therefore, applicant is only enabled for these specific antibodies for the first and second set of antibodies.

Response to Arguments

15. Applicant's arguments filed September 23, 2004 have been fully considered but they are not persuasive.

16. With respect to applicant's arguments regarding the rejection of claim 1 under 35 U.S.C. 112, second paragraph, over the term "normal", applicant has not established what parameters were used to select the healthy controls, rendering the term indefinite.

17. With respect to the arguments to the rejections under 35 U.S.C. 112, first paragraph, on page 6-7, applicant has only disclosed 8 specific antigens in fig. 6, and not for all antigens associated with cardiovascular and autoimmunity and autoimmune disease, as has been discussed above. Therefore claim 1 is still not enabled for all antigens associated with cardiovascular and autoimmunity and autoimmune disease.

18. Applicant's arguments with respect to claims 1-11 regarding the prior art have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (571) 272-0826. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V Le can be reached on (571)272-0823. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

21. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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12/13/04